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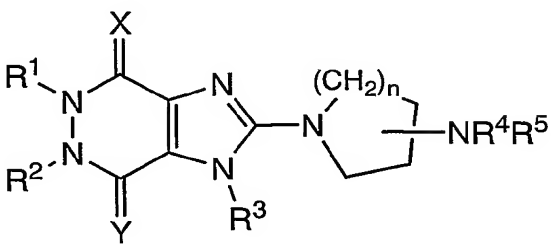
(54) Title: 1H-IMIDAZO'4,5-D!PYRIDAZINES AS DPP-IV INHIBITORS FOR THE TREATMENT OF NIDDM



(I)

(57) Abstract: A compound of the formula (I) or a pharmaceutically acceptable salt thereof: [wherein X and Y each is independently O, etc.; R^1 and R^2 each is independently H or (lower)alkyl; R^3 is (lower)alkenyl, etc; R^4 and R^5 each is independently H or (lower)alkyl; n is 0, 1, 2, 3 or 4.] Compound of formula (I) inhibit DPP-IV activity. They are therefore useful in the treatment of conditions mediated by DPP-IV, such as NIDDM.

DESCRIPTION

1H-IMIDAZO'4,5-D!PYRIDAZINES AS DPP-IV INHIBITORS FOR THE TREATMENT OF NIDDM

TECHNICAL FIELD

This invention relates to the compound and pharmaceutically acceptable salt thereof which inhibit dipeptidyl peptidase-IV (DPP-IV).

Moreover, this invention relates to medicament or pharmaceutical composition comprising the above-mentioned compound or pharmaceutically acceptable salt thereof as an active ingredient, a method for treatment and/or prevention of NIDDM, or the like, and use of the above compound.

BACKGROUND ART

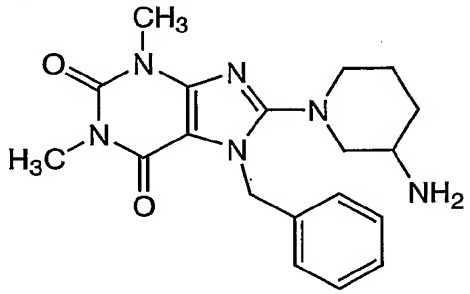
It is known that DPP-IV has various physiological functions in living body, especially has the action which inactivates Glucagon-like peptide-1 (GLP-1) by cleaving the terminal dipeptide (His-Ala). That is, the resultant peptide is the receptor antagonist of GLP-1 and totally reduces the activity of GLP-1.

This GLP-1 has very important role in sugar metabolism. For example, (1) GLP-1 intensifies the secretion of insulin, (2) express genes which are indispensable for the secretion of insulin, (3) stimulate proliferation of β-cell, (4) suppresses secretion of glucagon, (5) suppresses the function about secretion and motility of digestive organs (especially, peristalsis), and (6) suppresses appetite. That is, GLP-1 restricts food ingestion, postpones the process of digestion and absorption, and raised the use of the sugar in blood.

Therefore, the inhibitor of DPP-IV can maintain the activity of GLP-1, so it is expected as a medicine to treat and prevent various diseases, especially non-insulin

dependent diabetes mellitus (NIDDM).

Hitherto, such inhibitors of DPP-IV are known so far. For example, in WO02/068420, xanthine derivatives like following are disclosed.



DISCLOSURE OF INVENTION

Under the above situation, the inventors of this invention found that imidazopyridazine derivatives have remarkable activity to inhibit DPP-IV, and the inventors completed this invention.

Accordingly, this invention relates to DPP-IV inhibitor. More particularly, this invention relates to DPP-IV inhibitor useful for treating or preventing conditions mediated by DPP-IV, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus.

That is, one object of this invention is to provide new compound and pharmaceutically acceptable salt thereof, of which activity to inhibit DPP-IV is remarkably improved against known compounds.

Another object of this invention is to provide a medicament and pharmaceutical composition containing the compound and/or pharmaceutically acceptable salt thereof as an active ingredient.

A further object of this invention is to provide a inhibitor of DPP-IV and a method for inhibiting DPP-IV

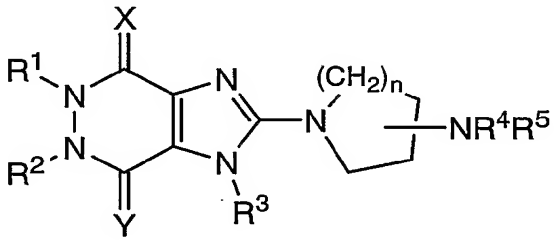
comprising administering an effective amount of the compound and/or pharmaceutically acceptable salt thereof.

A further object of this invention is to provide a use of the compound and pharmaceutically acceptable salt thereof as medicaments.

A further object of this invention is to provide the compound and pharmaceutically acceptable salt thereof which are useful for the manufacture of medicaments for treating or preventing conditions mediated by DPP-IV inhibition, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus, especially NIDDM.

A further object of this invention is to provide the commercial package comprising the pharmaceutical composition containing the new compound.

The compound of this invention can be represented by the following formula (I):



(I)

[wherein

X and Y each is independently O, S, NR^6 (R^6 is H, (lower)alkyl, hydroxy, (lower)alkoxy, cyano or carbamoyl) or CR^7R^8 (R^7 and R^8 each is independently H or (lower)alkyl);

R^1 and R^2 each is independently H or (lower)alkyl;

R^3 is H, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)acyl, aryl[(lower)alkyl] (which

may be substituted on the aryl group) or arylcarbonyl (which may be substituted on the aryl group);

R^4 and R^5 each is independently H or (lower)alkyl;

n is 0, 1, 2, 3 or 4;

the substituent(s) on the aryl is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, halogen, hydroxy, cyano, nitro, amino and carboxy.]

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Therefore, the "(lower)alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, and it is preferably (C1-C4)alkyl, more preferably (C1-C2)alkyl, most preferably methyl.

The "(lower)alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy, and the like, and it is preferably (C1-C4)alkoxy, more preferably (C1-C2)alkoxy, most preferably methoxy.

The "(lower)alkenyl" means a straight or branched chain aliphatic hydrocarbon having more than one double bond between two carbon atoms, such as ethenyl, 1-methylethenyl, 1-propenyl, 2-propenyl, 1-methyl-1-propenyl, 2-butenyl, 3-butenyl, 3-methyl-2-butenyl, pentenyl, hexenyl, and the like, and it is preferably (C2-C5)alkenyl, more preferably 3-methyl-2-butenyl.

The "(lower)alkynyl" means a straight or branched

chain aliphatic hydrocarbon having more than one triple bond between two carbon atoms, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like, and it is preferably (C2-C4)alkynyl, more preferably (C2-C3)alkynyl.

The "(lower)acyl" means a formyl and a (lower)alkyl carbonyl group such as acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, and the like, and it is preferably (C1-C4)acyl (including formyl), more preferably (C1-C2)acyl, most preferably acetyl.

The "aryl" means a C6-C10 aromatic hydrocarbon group, such as phenyl, naphthyl, indenyl, or the like, and it is preferably phenyl.

The "aryl[(lower)alkyl]" means the "(lower)alkyl" group mentioned above substituted by aryl group mentioned above, such as benzyl, 1-phenethyl, 2-phenethyl, 3-phenylpropyl, phenylisopropyl, 4-phenylbutyl, 6-phenylhexyl and the like, and it is preferably phenyl[(C1-C4)alkyl], more preferably phenyl[(C1-C2)alkyl], most preferably benzyl.

The "arylcarbonyl" means a carbonyl group substituted with aryl group mentioned above, such as benzoyl, naphthylcarbonyl, indenylcarbonyl, or the like, and it is preferably benzoyl.

The "aryl" may be substituted. The number of the substituent is preferably 1 to 4, more preferably 1 or 2, most preferably 1. In case that "aryl" has plural substituents, they may be the same or different from each other, but needless to say, "aryl" may not have substituent.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, it is preferably a chlorine atom.

The compound of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compound of the formula (I) may also exist in tautomeric forms and this invention includes both mixtures and separate individual tautomers.

The compound of the formula (I) and its salt may be in a form of a solvate such as hydrate, which is included within the scope of the present invention.

Also included in the scope of invention are radiolabelled derivatives of compound of formula (I) which are suitable for biological studies.

The compound of this invention can be converted to salt according to a conventional method. Suitable salts of the compound (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, or the like.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, or the like.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, or the like.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, or the like.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, or the like.), a salt with an amino acid (e.g., arginate, aspartate, glutamate, or the like.), or the like.

In the each definition of the compound formula (I), preferably,

(1) X and Y each is independently O, S or NR^6 (R^6 is H, (lower)alkyl, hydroxy, (lower)alkoxy, cyano or carbamoyl),

(2) X and Y each is independently O or S,

(3) X and Y are O,

(4) R^1 and R^2 each is independently (lower)alkyl,

(5) R^1 and R^2 each is independently (C1-C4)alkyl,

(6) R^1 and R^2 are methyl,

(7) R^3 is H, (lower)alkyl, (lower)alkenyl or (lower)alkynyl,

(8) R^3 is (lower)alkenyl,

(9) R^3 is (lower)acyl or arylcarbonyl (which may be substituted on the aryl group),

(10) R^3 is aryl[(lower)alkyl] (which may be substituted on the aryl group),

(11) R^3 is benzyl (which may be substituted on the phenyl group),

(12) R^4 and R^5 are H

(13) R^4 and R^5 each is independently (lower)alkyl,

(14) n is 0,

(15) n is 1,

(16) n is 2,

(17) the substituent(s) on the aryl is(are) selected from the group consisting of (lower)alkoxy, hydroxy and amino,

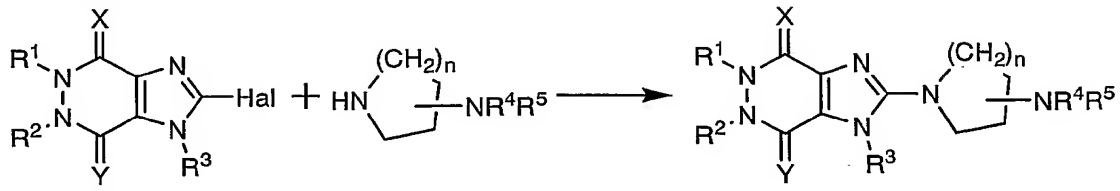
(18) the substituent(s) on the aryl is(are) (lower)alkyl,

(19) the substituent(s) on the aryl is(are) selected from the group consisting of halogen, cyano, nitro and carboxy,

(20) the substituent(s) on the aryl is(are) halogen.

The compound of the formula (I) of the present invention can be prepared according to the following Process A.

[Process A]



(II) (III) (I)

In the above formula, R^1 to R^5, X and Y represent the same meanings as defined above, and "Hal" represents halogen atom, especially, chlorine or bromine atom.

Process A is the process for preparing the compound (I). This process is carried out by reacting halogenated Compound (II) and amino Compound (III) in the presence of base in solvent.

Compound (II) may be purchased if it is commercial, or synthesized according to Process B mentioned after or other general methods obvious to the person skilled in the organic chemistry from commercial compounds. Compound (III) may be purchased if it is commercial or synthesized by general methods obvious to the person skilled in the organic chemistry from commercial compounds, since the structure of Compound (III) is relatively simple.

This process is generally carried out by adding Compound (III) and base to the solution of Compound (II).

The base employable in this Process is not particularly limited so long as it accelerates this reaction and may include alkali metal hydrogencarbonates such as litium hydrogencarbonate, sodium hydrogencarbonate and potassium hydrogencarbonate; alkali metal carbonates such as lithium carbonate, sodium carbonate and potassium carbonate; alkaline earth metal carbonates such as magnesium carbonate and calcium

carbonate; preferably alkali metal carbonates, especially potassium hydrogencarbonate.

The solvent employable in this Process is not particularly limited so long as it is inactive in this reaction and resolve moderately substrates, and may include dimehylsulfoxide; amide such as dimethylformamide, dimethylacetamide.

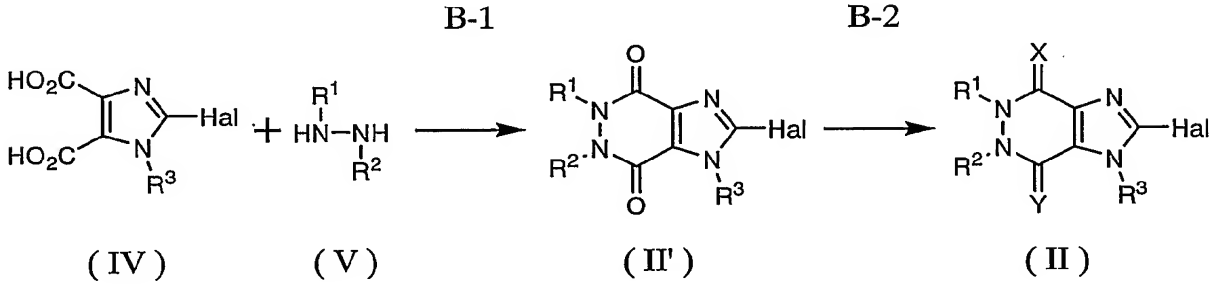
The temperature at that time varies depending on the starting material, the solvent, or the like, but it is usually 10℃ to room temperature. After the addition of Compound (III) and base, the temperature may be raised.

The reaction time after the addition varies depending on the starting material, the solvent, or the like, but it is usually from 1hr to 24hrs, preferably 2hrs to 12hrs.

After the reaction, the mixture is diluted with organic solvent insoluble with water such as ethyl acetate, chloroform, or the like, and the organic layer is washed by water, brine, or the like. The organic layer is dried over anhydrous magnesium sulfate or sodium sulfate, and evaporated in vacuo. The target compound is purified by the conventional method such as silica gel column chromatography, or the like from the residue.

Compound (II), which is the starting compound of Process A, can be synthesized by following Process B.

[Process B]



(IV) (V) (II') (II)

In the above formula, R^1 to R^3, X, Y and Hal represent the same meanings as defined above.

Process B is the process for preparing the compound (II), which is the starting material of Process A. First, this process is carried out by condensating dicarboxylic acid Compound (IV) and hydrazine Compound (V) by general condensating method, for example, by using condensating agent and activating agent. Then, if necessary, carbonyl group(s) of pyridazinedione ring is(are) transformed.

Compound (IV) may be purchased if it is commercial, or synthesized according to Process C mentioned after or other general methods obvious to the person skilled in the organic chemistry from commercial compounds. Compound (V) may be purchased if it is commercial or synthesized by general methods obvious to the person skilled in the organic chemistry from commercial compounds, since the structure of Compound (V) is relatively simple.

In the case that condensing agent is used, the condensing agent employable in this process is not particularly limited so long as it accelerates forming amide bond and may include carbodiimide compounds such as dicyclohexylcarbodiimide (DCC), diisopropyl-carbodiimide (DIPCI), water solvable carbodiimide (WSCD) such as 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide.

In the case, catalyst is generally used. The catalyst employable in this process is not particularly limited so long as it can mainly make the carboxyl groups of Compound (IV) active and may include 1-hydroxybenzotriazole (HOBt), 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazole (HOOBt), 1-hydroxy-7-azabenzotriazole (HOAt).

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include amides such as dimethylformamide and dimethylacetamide; alcohol such as methanol and ethanol.

This process is generally carried out by adding Compound (V), condensing agent and catalyst to the solution of Compound (IV).

The temperature at that time varies depending on the starting material, the solvent, or the like, but it is usually room temperature.

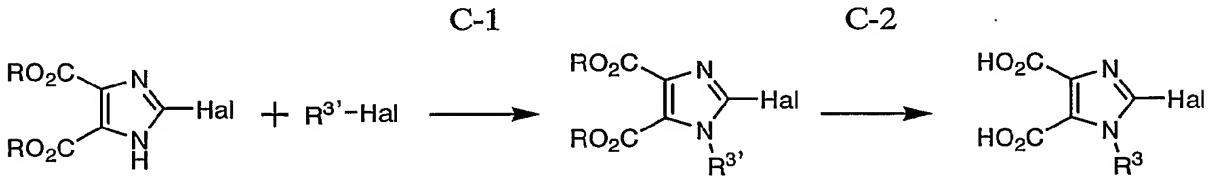
The reaction time after the adding varies depending on the starting material, the solvent, or the like, but it is usually from 1hr to 30hrs.

After the reaction, the mixture is diluted with organic solvent insoluble with water such as ethyl acetate, chloroform, or the like, and the organic layer is washed by water, brine, or the like. The organic layer is dried over anhydrous magnesium sulfate or sodium sulfate, and evaporated in vacuo. The target compound is purified by the conventional method such as recrystallization to obtain Compound (II').

Then, if necessary, the carbonyl group(s) in pyridazinedione ring of Compound (II') by ordinary functional group transformation reaction.

Compound (IV), which is the starting compound of Process B, can be synthesized by following Process C.

[Process C]



(VI) (VII) (VI') (IV)

In the above formula, R^3 and Hal represent the same meanings as defined above. R represents (lower)alkyl, especially, methyl, ethyl or tert-butyl, and $R^{3'}$ is R^3 defined above except H.

Process C is the process for preparing the compound

(IV), which is the starting material of Process B. First, in case that Compound (IV) of which R^3 is not H is necessary, R^3 group is introduced. Then, Compound (VI) or (VI') is hydrolyzed.

Compound (VI) may be purchased if it is commercial, or synthesized by general methods obvious to the person skilled in the organic chemistry from imidazole dicarboxylic acid derivative.

Process C-1 is carried out by reacting imidazole Compound (VI) and halogenated Compound (VII) in the presence of base in solvent. This process is generally carried out by adding Compound (VII) and base to the solution of Compound (VI).

The base employable in this process is not particularly limited so long as it accelerates this process and may include organic amines such as triethylamine, tributylamine, diisopropylethylamine (DIEA), preferably DIEA.

The solvent employable in this Process is not particularly limited so long as it is inactive in this reaction and resolves moderately substrates, and may include amide such as dimethylformamide and dimethylacetamide.

The temperature at that time varies depending on the starting material, the solvent, or the like, but it is usually room temperature.

The reaction time after the addition varies depending on the starting material, the solvent, or the like, but it is usually from 1hr to 24hrs, preferably 2hrs to 12hrs.

After the reaction, the mixture is diluted with organic solvent insoluble with water such as ethyl acetate, chloroform, or the like, and the organic layer is washed by water, brine, or the like. The organic layer is dried over anhydrous magnesium sulfate or sodium sulfate, and evaporated in vacuo. The target compound is purified by

the conventional method such as silica gel column chromatography, or the like from the residue.

In Process C-2, general hydrolysis reaction is employable. For example, the solution of Compound (VI) or (VI') in aqueous sodium hydroxide is refluxed. After the reaction, Compound (IV) as solid can be obtained by acidifying the solution.

Above processes, all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method.

In case that at least one of R^1 to R^6 bound nitrogen atom is H, the amino group may be protected and the protective group may be timely cleaved. Concerning the kind of protective group and the reactive condition of the formation and cleavage, 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John Wiley & Sons, INC. may be referred.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

THE BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Although the present invention has been fully described by way of example, it is to be understood that various changes and modifications will be apparent to those skilled in the art. Therefore, unless otherwise such changes and modifications depart from the scope of the present invention hereinafter defined, they should be construed as being included therein.

Preparation 1
Dimethyl 2-bromo-1H-imidazole-4,5-dicarboxylate

To a solution of dimethyl 1H-imidazole-4,5-dicarboxylate (1.58g) in water (15mL), was added bromine (4.11g). The mixture was stirred at 60℃ for 1hr.

The solvent was evaporated in vacuo and the residue was triturated with ether to give the target compound (2.35g) as a solid.

NMR (DMSO-d_6) : δ 3.81(6H, s).
MASS m/z : 286 (M-1).

Example 1-1
Dimethyl 2-bromo-1-(2-chlorobenzyl)-1H-imidazole-4,5-dicarboxylate

To a solution of dimethyl 2-bromo-1H-imidazole-4,5-dicarboxylate obtained in Preparation 1 (261mg) in dimethylformamide (3mL), was added 2-chlorobenzyl bromide (218mg) and N,N-diisopropylethylamine (0.28mL), and the mixture was stirred at room temperature for 4hrs.

The resulting mixture was diluted with ethyl acetate, and washed successively water and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with chloroform and ethyl acetate (4:1) to give the target compound (146mg).

NMR ($CDCl_3$) : δ 3.81(3H, s), 3.94(3H, s), 5.57(2H, s), 6.52(1H, dd, J=2,8Hz), 7.13-7.48(2H, m), 7.42(1H, dd, J=2,8Hz).

Example 1-2
2-Bromo-1-(2-chlorobenzyl)-1H-imidazole-4,5-dicarboxylic acid

To a solution of dimethyl 2-bromo-1-(2-chlorobenzyl)-1H-imidazole-4,5-dicarboxylate obtained in Example 1-1 (146mg) in ethanol (5mL), was added 1N sodium hydroxide (0.90mL). The mixture was stirred at reflux for 40min.

The solvent was evaporated in vacuo. The residue was diluted with water and added 1N hydrochloric acid (1.1mL). The resulting solid was collected and washed with water to give the target compound (121mg).

NMR (DMSO-d_6) : δ 5.72(2H, s), 6.39(1H, dd, J=2,8Hz), 7.22-7.36(2H, m), 7.50(1H, dd, J=2,8Hz).
MASS (m/z) : 356.95, 358.97 (M-1).

Example 1-3
2-Bromo-1-(2-chlorobenzyl)-5,6-dimethyl-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione

To a solution of 2-bromo-1-(2-chlorobenzyl)-1H-imidazole-4,5-dicarboxylic acid

obtained in Example 1-2 (106mg) in dimethylformamide (3mL), was added 1-hydroxy-7-azabenzotriazole (112mg), 1,2-dimethylhydrazine dihydrochloride (43.1mg) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (128mg). The mixture was stirred at room temperature for 14hrs.

The resulting mixture was diluted with ethyl acetate, and washed successively with water and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was recrystallized from methanol to give the target compound (51mg) as a colorless crystal.

NMR (DMSO-d_6) : δ 3.59(3H, s), 3.64(3H, s), 5.75(2H, s), 6.54(1H, dd, J=8Hz), 7.22-7.58(2H, m), 7.55(1H, dd, J=8Hz).
MASS (m/z) : 383.03, 384.94 (M+1).

Example 1-4
tert-Butyl (3S)-1-[1-(2-chlorobenzyl)-5,6-dimethyl-4,7-dioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl]-3-piperidinylcarbamate

To a solution of 2-bromo-1-(2-chlorobenzyl)-5,6-dimethyl-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione obtained in Example 1-3 (45mg) in dimethylsulfoxide (1.5mL), was added tert-butyl (3S)-3-piperidinylcarbamate (28.3mg) and potassium carbonate (22.7mg). The mixture was stirred at 100℃ for 5hrs.

The resulting mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel eluting with chloroform and methanol (9:1) to give the target compound (36.8mg).

NMR ($CDCl_3$) : δ 1.42(9H, s), 1.45(1H, m), 1.54-1.72(2H, m), 1.78(1H, m), 2.89-3.10(3H, m), 3.42(1H, m), 3.63(3H, s), 3.72(3H, s), 3.73(1H, m), 4.67(1H, m), 5.58(1H, d, J=20Hz), 5.77(1H, d, J=20Hz), 6.64(1H, d, J=8Hz), 7.13-7.25(2H, m), 7.42(1H, dd, J=2,8Hz).
MASS (m/z) : 503 (M+1).

Example 1-5
2-[(3S)-3-Amino-1-piperidinyl]-1-(2-chlorobenzyl)-5,6-dimethyl-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione dihydrochloride

To a solution of tert-butyl (3S)-1-[1-(2-chlorobenzyl)-5,6-dimethyl-4,7-dioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl]-3-piperidinylcarbamate obtained in Example 1-4 (36.8mg) in dichloromethane (1mL), was added 4N hydrogen chloride in dioxane (0.4mL). The mixture was stirred at room temperature for 1hr.

The solvent was evaporated in vacuo and the residue was triturated with dichloromethane to give the target compound (22mg) as a solid.

NMR (DMSO-d_6) : δ 1.38-1.60(2H, m), 1.73(1H, m), 1.94(1H, m), 2.77(1H, m), 2.96-3.13(2H, m), 3.28(1H, m), 3.54(3H, s), 3.56(1H, m), 3.61(3H, s), 5.56(2H, m), 6.72(1H, d, J=8Hz), 7.21-7.54(2H, m), 7.50(1H, dd, J=2,8Hz).
MASS (m/z) : 403 (free+1).

Example 2-1
Dimethyl 2-bromo-1-(3-methyl-2-butenyl)-1H-imidazole-4,5-dicarboxylate

The title compound (1.31g) was prepared from dimethyl

2-bromo-1H-imidazole-4,5-dicarboxylate obtained in Preparation 1 in a similar manner to that of Example 1-1.

NMR ($CDCl_3$) : δ 1.73(3H, s), 1.77(3H, s), 3.91(3H, s), 3.92(3H, s), 4.83(2H, d, J=7Hz), 5.13(1H, m).
MASS (m/z) : 330.99, 333.00 (M+1).

Example 2-2
2-Bromo-1-(3-methyl-2-butenyl)-1H-imidazole-4,5-dicarboxylic acid

The title compound (1.1g) was prepared from dimethyl 2-bromo-1-(3-methyl-2-butenyl)-1H-imidazole-4,5-dicarboxylate obtained in Example 2-1 in a similar manner to that of Example 1-2.

NMR (DMSO-d_6) : δ 1.69(3H, s), 1.77(3H, s), 4.95(2H, d, J=7Hz), 5.12(1H, m).
MASS (m/z) : 301.03, 303.03 (M-1).

Example 2-3
2-Bromo-5,6-dimethyl-1-(3-methyl-2-butenyl)-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione

The title compound (190mg) was prepared from 2-bromo-1-(3-methyl-2-butenyl)-1H-imidazole-4,5-dicarboxylic acid obtained in Example 2-2 in a similar manner to that of Example 1-3.

NMR ($CDCl_3$) : δ 1.74(3H, s), 1.87(3H, s), 3.69(3H, s), 3.71(3H, s), 5.11(2H, d, J=7Hz), 5.26(1H, m).
MASS (m/z) : 327.03, 329.00 (M+1).

Example 2-4
tert-Butyl (3S)-1-[5,6-dimethyl-1-(3-methyl-2-buteny

1)-4,7-dioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl]-3-piperidinylcarbamate

The title compound (148mg) was prepared from 2-bromo-5,6-dimethyl-1-(3-methyl-2-butenyl)-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione obtained in Example 2-3 in a similar manner to that of Example 1-4.

NMR ($CDCl_3$) : δ 1.44(9H, s), 1.45(1H, m), 1.58-1.97(3H, m), 1.74(3H, s), 1.80(3H, s), 2.83-3.27(3H, m), 3.48(1H, m), 3.66(3H, s), 3.70(3H, s), 3.83(1H, m), 4.78(1H, m), 4.88(2H, m), 5.34(1H, m).
MASS (m/z) : 447 (M+1).

Example 2-5
2-[(3S)-3-Amino-1-piperidinyl]-5,6-dimethyl-1-(3-methyl-2-butenyl)-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione dihydrochloride

The title compound (111mg) was prepared from tert-butyl (3S)-1-[5,6-dimethyl-1-(3-methyl-2-butenyl)-4,7-dioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl]-3-piperidinylcarbamate obtained in Example 2-4 in a similar manner to that of Example 1-5.

NMR ($DMSO-d_6$) : δ 1.55-1.70(2H, m), 1.69(3H, s), 1.76(3H, s), 1.87(1H, m), 2.03(1H, m), 2.88(1H, m), 3.06(1H, m), 3.17(1H, m), 3.37(1H, m), 3.52(1H, m), 3.60(6H, s), 4.86(2H, m), 5.32(1H, m).
MASS (m/z) : 347 (free+1).

Example 3-1
Dimethyl 1-benzyl-2-bromo-1H-imidazole-4,5-dicarboxylate

The title compound is prepared from dimethyl 2-bromo-1H-imidazole-4,5-dicarboxylate obtained in Preparation 1 and benzyl bromide in a similar manner to that of Example 1-1.

NMR ($CDCl_3$) : δ 3.82(3H, s), 3.92(3H, s), 5.48(2H, s), 7.08(2H, dd, J=2,8Hz), 7.26-7.36(3H, m).
MASS (m/z) : 353.02, 355.00 (M+1).

Example 3-2
1-Benzyl-2-bromo-1H-imidazole-4,5-dicarboxylic acid

The title compound is prepared from dimethyl 1-benzyl-2-bromo-1H-imidazole-4,5-dicarboxylate obtained in Example 3-1 in a similar manner to that of Example 1-2.

NMR (DMSO-d_6) : δ 5.67(2H, s), 7.05(2H, d, J=8Hz), 7.24-7.40(3H, m).
MASS (m/z) : 323.03, 325.04 (M-1).

Example 3-3
1-Benzyl-2-bromo-5,6-dimethyl-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione

The title compound is prepared from 1-benzyl-2-bromo-1H-imidazole-4,5-dicarboxylic acid obtained in Example 3-2 in a similar manner to that of Example 1-3.

NMR ($CDCl_3$) : δ 3.69(3H, s), 3.72(3H, s), 5.72(2H, s), 7.26-7.38(5H, m).
MASS (m/z) : 349.04, 351.05 (M+1).

Example 3-4

tert-Butyl [(3S)-1-(1-benzyl-5,6-dimethyl-4,7-dioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl)-3-piperidinyl]carbamate

The title compound is prepared from 1-benzyl-2-bromo-5,6-dimethyl-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione obtained in Example 3-3 in a similar manner to that of Example 1-4.

NMR ($CDCl_3$) : δ 1.43(9H, s), 1.47(1H, m), 1.58-1.92(3H, m), 2.94(1H, m), 2.98-3.15(2H, m), 3.45(1H, m), 3.65(3H, s), 3.70(3H, s), 3.77(1H, m), 4.64(1H, m), 5.46(1H, d, J=20Hz), 5.68(1H, d, J=20Hz), 7.15(2H, d, J=8Hz), 7.26-7.75(3H, m).
MASS (m/z) : 469 (M+1).

Example 3-5
2-[(3S)-3-Amino-1-piperidinyl]-1-benzyl-5,6-dimethyl-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione dihydrochloride

The title compound is prepared from tert-butyl [(3S)-1-(1-benzyl-5,6-dimethyl-4,7-dioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl)-3-piperidinyl]carbamate obtained in Example 3-4 in a similar manner to that of Example 1-5.

NMR (DMSO-d_6) : δ 1.42-1.61(2H, m), 1.76(1H, m), 1.96(1H, m), 2.74(1H, m), 3.00-3.10(2H, m), 3.33(1H, m), 3.54(1H, m), 3.58(3H, s), 3.60(3H, s), 5.56(2H, s), 7.15(2H, d, J=8Hz), 7.21-7.37(3H, m).
MASS (m/z) : 369 (free+1).

Example 4-1
tert-Butyl {(3R)-1-[5,6-dimethyl-1-(3-methyl-2-buten-

1-yl)-4,7-dioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl]-3-piperidinyl}carbamate

The title compound is prepared from 2-bromo-5,6-dimethyl-1-(3-methyl-2-butenyl)-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione obtained in Example 2-3 in a similar manner to that of Example 1-4.

NMR ($CDCl_3$) : δ 1.44(9H, s), 1.45(1H, m), 1.58-1.97(3H, m), 1.74(3H, s), 1.80(3H, s), 2.83-3.27(3H, m), 3.48(1H, m), 3.66(3H, s), 3.70(3H, s), 3.83(1H, m), 4.78(1H, m), 4.88(2H, m), 5.34(1H, m).
MASS (m/z) : 447 (M+1).

Example 4-2
2-[(3R)-3-Amino-1-piperidinyl]-5,6-dimethyl-1-(3-methyl-2-buten-1-yl)-5,6-dihydro-1H-imidazo[4,5-d]pyridazine-4,7-dione dihydrochloride

The title compound is prepared from tert-butyl {(3R)-1-[5,6-dimethyl-1-(3-methyl-2-buten-1-yl)-4,7-dioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl]-3-piperidinyl}carbamate obtained in Example 4-1 in a similar manner to that of Example 1-5.

NMR (DMSO-d_6) : δ 1.55-1.70(2H, m), 1.69(3H, s), 1.76(3H, s), 1.87(1H, m), 2.03(1H, m), 2.88(1H, m), 3.06(1H, m), 3.17(1H, m), 3.37(1H, m), 3.52(1H, m), 3.59(6H, s), 4.86(2H, m), 5.32(1H, m).
MASS (m/z) : 347 (free+1).

Example 5-1
tert-Butyl {(3R)-1-[5,6-dimethyl-1-(3-methyl-2-buten-1-yl)-7-oxo-4-thioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl]-3-piperidinyl}carbamate

To a solution of tert-butyl (3R)-1-[5,6-dimethyl-1-(3-methyl-2-butenyl)-4,7-dioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl]-3-piperidinylcarbamate obtained in Example 4-1 (80mg) in toluene (3.0mL), was added Lawesson's Reagent (36.2mg). The mixture was stirred at 110℃ for 30min.

The resulting mixture was evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexane and ethyl acetate (1:1) to give the target compound (67mg).

NMR ($CDCl_3$) : δ 1.44(9H, s), 1.45(1H, m), 1.58-1.97(3H, m), 1.73(3H, s), 1.79(3H, s), 3.00-3.32(3H, m), 3.52(1H, m), 3.81(3H, s), 4.28(3H, s), 3.83(1H, m), 4.78(2H, m), 4.88(2H, m), 5.30(1H, m).
MASS (m/z) : 463 (M+1).

Example 5-2

2-[(3R)-3-Amino-1-piperidinyl]-5,6-dimethyl-1-(3-methyl-2-buten-1-yl)-7-thioxo-1,5,6,7-tetrahydro-4H-imidazo[4,5-d]pyridazin-4-one dihydrochloride

The title compound is prepared from tert-butyl {(3R)-1-[5,6-dimethyl-1-(3-methyl-2-buten-1-yl)-7-oxo-4-thioxo-4,5,6,7-tetrahydro-1H-imidazo[4,5-d]pyridazin-2-yl]-3-piperidinyl}carbamate obtained in Example 5-1 in a similar manner to that of Example 1-5.

NMR (DMSO-d_6) : δ 1.55-1.70(2H, m), 1.69(3H, s), 1.76(3H, s), 1.87(1H, m), 2.03(1H, m), 2.89(1H, m), 3.11(1H, m), 3.22(1H, m), 3.37(1H, m), 3.56(1H, m), 3.76(3H, s), 4.23(3H, s), 4.84(2H, m), 5.32(1H, m).
MASS (m/z) : 363 (free+1).

In order to illustrate the usefulness of the object Compound (I), the pharmacological test is carried out as shown in the following.

[A] Inhibition test of human plasma DPP-IV :

(i) Material and Method :

The effect of test compounds on DPP-IV activity in human plasma was evaluated with a modified version of the assay described by Hughes et al (Biochemistry, 38, pp11597-11603(1999)).

Briefly, 20μL of human plasma were mixed with 20 μL of 80mM $MgCl_2$ in assay buffer (25mM HEPES, 140mM NaCl, 1% RIA-grade BSA, pH7.8), and were incubated in a room temperature for 60min. Then the reaction was initiated by the addition of both 20μL of test compounds and 20 μL of 0.2mM substrate (H-glycine-proline-AMC; AMC is 7-amino-4-methylcoumarine), they were dissolved in the assay buffer.

After 20min incubation in a room temperature (kept in the dark), fluorescence was measured (Excitation 380nm, Emission 460nm). A fluorescence-concentration curve of free AMC was obtained using AMC solution in the assay buffer with appropriate concentration. Plasma DPP-IV activities, with or without the test compounds, were expressed as the amount of product per minute per mL. The potency of the test compounds as DPP-IV inhibitor was expressed as IC_{50}.

It appeared, from the above-mentioned Inhibition test, that the compound (I) or pharmaceutically acceptable salt thereof of the present invention have an inhibiting activity against DPP-IV. Therefore, the compound (I) or pharmaceutically acceptable salt thereof are useful for treating or preventing disease mediated by DPP-IV, more particularly useful for treating or preventing altered

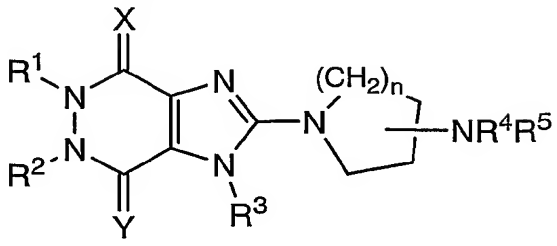
glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus.

The patents, patent applications and publications cited herein are incorporated by reference.

This application is based on Australian Provisional Application No.2003902828 filed on June 5, 2003, the contents of which are hereby incorporated by references.

C L A I M S

1. A compound of the formula (I) or pharmaceutically acceptable salt thereof.



(I)

[wherein

X and Y each is independently O, S, NR^6 (R^6 is H, (lower)alkyl, hydroxy, (lower)alkoxy, cyano or carbamoyl) or CR^7R^8 (R^7 and R^8 each is independently H or (lower)alkyl);

R^1 and R^2 each is independently H or (lower)alkyl;

R^3 is H, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)acyl, aryl[(lower)alkyl] (which may be substituted on the aryl group) or arylcarbonyl (which may be substituted on the aryl group);

R^4 and R^5 each is independently H or (lower)alkyl;

n is 0, 1, 2, 3 or 4;

the substituent(s) on the aryl is(are) selected from the group consisting of (lower)alkyl, (lower)alkoxy, halogen, hydroxy, cyano, nitro, amino and carboxy]

2. The compound of Claim 1, wherein X and Y each is independently O or S.

3. The compound of Claim 1, wherein X and Y are O.

4. The compound of any one of Claim 1 to 3, wherein R^1 and R^2 each is independently (C1-C4)alkyl.

5. The compound of any one of Claim 1 to 4, wherein R^3 is benzyl (which may be substituted on the phenyl group).

6. The compound of any one of Claim 1 to 4, wherein R^3 is (lower)alkenyl.

7. The compound of any one of Claim 1 to 6, wherein R^4 and R^5 are H.

8. The compound of any one of Claim 1 to 7, wherein n is 2.

9. A medicament comprising a compound of any one of Claim 1 to 8 as an active ingredient.

10. A pharmaceutical composition comprising a compound of any one of Claim 1 to 8 as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient.

11. An inhibitor of DPP-IV consisting of a compound of any one of Claim 1 to 8.

12. A method for treatment and/or prevention of NIDDM which comprises administering an effective amount of the compound of any one of Claim 1 to 8 to human beings or animals.

13. The compound of any one of Claim 1 to 8 for use in the treatment and/or prevention of NIDDM in human beings or animals.

14. Use of the compound of any one of Claim 1 to 8 for the manufacture of a medicament for treatment and/or prevention of NIDDM in human beings or animals.

15. A commercial package comprising the pharmaceutical

composition containing the compound (I) identified in any one of Claim 1 to 8 and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating NIDDM.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/JP2004/007996

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/5025 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/004496 A (NOVO NORDISK AS) 16 January 2003 (2003-01-16) the whole document	1-15
E	WO 2004/050658 A (BOEHRINGER INGELHEIM PHARMA ; ECKHARDT MATTHIAS (DE); HIMMELSBACH FRAN) 17 June 2004 (2004-06-17) the whole document	1-15
E	US 2004/116328 A1 (CLARK RICHARD ET AL) 17 June 2004 (2004-06-17) the whole document & WO 03/104229 A (KIRA KAZUNOBU ; RICHARD CLARK (JP); EISAI CO LTD (JP); EMORI EITA (JP)) 18 December 2003 (2003-12-18)	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2004	08/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Grassi, D

INTERNATIONAL SEARCH REPORT

nformation on patent family members

Int ional Application No
PCT/JP2004/007996

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WO 2004050658 A	17-06-2004	DE 10256264 A1	24-06-2004
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